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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,449	11/17/2003	Ruben Laguens	42597-193226	9366

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VENABLE LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	
MAIL DATE	**DELIVERY MODE**
10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,449	LAGUENS ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,19-27,31,33-62,64-66,69,71-80 and 98-104* is/are pending in the application.

4a) Of the above claim(s) *3,5-9 and 45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,10-14,19-27,31,33-44,48-62,64-66,69,71-80 and 98-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 06/29/07 has been acknowledged.

Claims 1-14, 19-27, 31, 33-62, 64-66, 69, 71-80 and 98-104 are pending.

Earlier the applicant elected Group II that limits the invention to a method of inducing cardiomyogeneis by administering a polynucleotide encoding VEGF.

This application contains claims 3, 5, 6-9 and 45-47 are drawn to an invention nonelected with traverse in the reply filed on 10/26/06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-2, 4, 10-14, 19-27, 31, 33-44, 48-62, 64-66, 69, 71-80 and 98-104 are examined in this office action.

Claim Objections

Claim 1 is objected to because of the following informalities: The instant claim is drawn to non-elected subject matter, wherein the elected subject matter is a method of inducing cardiomyogeneis by administering a polynucleotide encoding VEGF. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1-2, 4, 10-14, 19-27, 31, 33-44, 48-62, 64-66, 69, 71-80 and 98-104 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reason of record as set forth in the office action mailed on 01/29/07.

Response to Argument (enablement)

Regarding the scope of the VEGF nuclotides the applicant argues that the claims recite VEGF-165 or an active site thereof. The applicant argues that VEGF has been studied extensively, and a skilled worker can readily determine which sequences

of the protein contain an active site. Therefore, the use of a polynucleotide encoding VEGF-165 or an active site thereof is fully supported by the specification.

However the applicant's arguments are found not persuasive because besides the pUVEK15 plasmid which encodes the human 165 amino acid VEGF polypeptide represented by SEQ ID NO: 1, the specification fails to disclose any variant of VEGF-165, which is capable of inducing the alleged cardiomyogeneis.

Regarding the scope of vector used the applicant argues that the claims have been amended to recite that the vector is a plasmid vector, in which inserted coding sequences are expressed under the control of a CMV promoter. Furhtermore regarding the route of administration the applicant argues that any route that delivers a polynucleotide to cardiomyocytes or tissues comprising cardiomyocytes (the currently elected species) is enabled by the specification. the applicant argues that such routes include, e.g., intravascular, intravenous, intra-arterial, intracardiac, intrapericardial, intramuscular, or a variety of other routes of administration. See delivery options for implementing myocardial gene transfer (Isner, *Nature* 415, 234-239, 2002)

However the applicant's arguments are found not persuasive. The applicnat fails to consider that one of the greatest challenges facing gene therapy is the efficient transfer and stable expression of transgenes in appropriate tissues. Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacles to overcome. The vector particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets. In the instant case the scope of invention as claimed is not limited to direct injection of the plasmid vector encoding the VEGF-165, which renders the invention as claimed unpredictable because for example the systemic administration to the plasmid vector would not result in the trasnsfection of cardiomyocytes in order to elicit the asserted therapeutic effects.

Therefore the earlier office action provides a clear reasoning that although the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals.

Regarding the unpredictability of the invnetion as claimed the applicant argues that the specification shows that the method of the present claims can induce cardiomyogenesis in a large mammal (pig) model. The applicant furhter argues that a recent publication (post filing publication) by the present inventors and colleagues (*Vera Janavel et al. Gene Ther. 13:1133-42, 2006*) confirms that in a large animal model (sheep) that a method of the invention successfully induces mitosis of cardiomyocytes and a reduction of infarct size.

However the applicant's arguments are found not persuasive because the publication of Vera Janavel et al. Gene Ther. 13:1133-42, 2006 is about 3 years after the filig date of instant invention ans the MPEP clealry states that the specification must be enabling as of the filing date see MPEP 2164.05. The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application"). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. In re Gunn, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); In re Budnick, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976) (In general, if an applicant seeks to use a patent to prove the state of the art for the purpose of the enablement requirement, the patent must have an issue date earlier than the effective filing date of the application.). While a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling, applicant can offer the testimony of an expert based on the publication as evidence of the level of skill in the art at the time the application was filed. Gould v. Quigg, 822 F.2d 1074, 1077, 3 USPQ2d 1302, 1304 (Fed. Cir. 1987).

Given the scope of invention as claimed the specification as filed fails to disclose the treatment of ischemic heart disease, myocardial infarction, myocardial ischemia, dilated cardiomyopathy, or hypertrophic cardiomyopathy by inducing cardiomyogeneisis via method as claimed, wherein the plasmid vector is administered via an intravascular, intracelomic, intramuscular or intracardiac administration. In the instant case the specification as filed fails to disclose that even genetic modification of cardiomyocytes with a polynucleotide encoding VEGF-165 or any variant thereof induces mitosis or proliferation of cardiomyocytes. Furthermore, inducing cardiomyogenesis by transfecting cardiomyocytes with a polynucleotide encoding VEGF-165 or any variant thereof, wherein the vector is administered via any and all route of administration is not considered routine in the art and without sufficient evidence provided in the specification as filed the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 57 and 66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 57 and 66 recites the limitation " VEGF1-165". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

Claims 1-2, 4, 10-14, 19-27, 31, 33-44, 48-62, 64-66, 69, 71-80 and 98-104 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Vale et al (Circ. 102:965-974, 2000).

Response to Argument (prior art)

The applicant argues that Vale et al does not teach or suggest that the dose of VEGF-165 which is administered therein is effective to induce cardiomyogenesis. The applicant argues that in order to demonstrate this Vale et al would have had to demonstrate an increased mitotic index, and/or a reduction in the size of infarcted tissue. the applicant argues that the induction of cardiomyogenesis is much more difficult to accomplish than merely restoring function to ischemic tissue; different dosing would be required to achieve these different effects. The applicant argues that recited dosages are lower dosages as compare to Vale et al.

However the applicant's arguments are found not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (*i.e. myocardial infraction, and/or Vale needs to demonstrate an increased mitotic index, and/or a reduction in the size of infarcted tissue*) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore Vale et al clearly teaches a gene therapy method that assess efficacy of phVEGF(165) gene transfer in chronic myocardial ischemia. The cited art teaches that the present study constitute additional objective evidence that $phVEGF_{165}$ GTx augments perfusion of ischemic myocardium, and the results also support the notion that $phVEGF_{165}$ GTx successfully rescued foci of hibernating myocardium. The cited art further teaches that the foci of ischemic myocardium, identified by preserved viability associated with impaired LLS, ie, electromechanical uncoupling, were demonstrated in all patients before GTx. The cited art teaches that the mean LLS in

areas of myocardial ischemia, improved significantly from 9.94±1.53% before phVEGF$_{165}$ GTx to 15.26±0.98% after phVEGF$_{165}$ GTx (*P*=0.004). In addition the area of ischemic myocardium was consequently reduced from 6.45±1.37 cm^2 before phVEGF$_{165}$ GTx to 0.95±0.41 cm^2 after GTx (*P*=0.001), see page 967 col. 2 and Table 2. The cited art further provided examples of NOGA maps showing septal, lateral, anterior, and inferior ischemic zones before GTx with improvement after GTx are shown in panel A of Figures 1 through 5 (see pages 968-972). The cited art further teaches the collated electrical and mechanical results of percutaneous EMM provide both an assessment of myocardial viability (ie, the presence of normal versus reduced voltage) and wall motion (presence of normal versus reduced fractional shortening). The cited art teaches that the analysis of LLS in areas of myocardial ischemia, documented marked improvement after GTx. Consequently, the area of ischemic myocardium was reduced to a statistically significant extent. Furthermore the corresponding NOGA maps likewise showed reduced evidence of ischemia after GTx. EMM provides separate assessments of viability (endocardial voltage recording) and function (LLS). Thus, those areas of the NOGA map that showed viable myocardium with impaired function before GTx versus viable myocardium with improved function after GTx support the notion that the defects that resolved on the SPECT scans constitute sites of hibernating myocardium that have been resuscitated.

Therefor the cited art clearly provides evidence regarding the recovery of cardiac tissue that comprises the cardiomyocytes. The reduction of ischemic myocardium *inherently* induces cardiomyogenesis cell proliferation and/or mitosis. The applicant fails to consider Kajstura et al, Proc Natl Acad Sci U S A. 95(15):8801-5, 1998, who teaches that it has been even well established that by confocal microscopy that 14 myocytes per million were in mitosis in control human hearts. A nearly 10-fold increase in this parameter was measured in end-stage ischemic heart disease (152 myocytes per million) and in idiopathic dilated cardiomyopathy (131 myocytes per million). Because the left ventricle contains 5.8 x 10(9) myocytes, these mitotic indices imply that 81.2 x 10(3), 882 x 10(3), and 760 x 10(3) myocytes were in mitosis in the entire ventricular

myocardium of control hearts and hearts affected by ischemic and idiopathic dilated cardiomyopathy, respectively (see Kajstura et al, page 8803, fig-2, page 8904 col.1-2).

Furthermore regarding the dose, it is well settled that routine optimization is not patentable, even if it results in significant improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955): Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. In instant case the modification as claimed in the instant invention encompasses obvious variations over cited prior art of record, which is well within the reach of one ordinary skilled in the art. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one skilled in the art. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added). With regards to determining experimental parameters, such as time in culture, the court has held that "[d]iscovery of optimum value of result effective variable in known process is ordinarily within skill of art (*In re Boesch and Slaney*, 205 USPQ 215 (CCPA 1980). Thus given the broadest

reasonable interpretation the invention as claimed is prima facie obvious if not anticipated in view of cited prior art of record.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUMESH KAUSHAL
PRIMARY EXAMINER